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Rapidly Progressive Corticobasal Degeneration Syndrome

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Key Words

Corticobasal syndrome · Creutzfeldt-Jakob disease · Diffusion-weighted images · Neuropathology · Alien hand phenomenon

Abstract

Introduction: Corticobasal syndrome (CBS) has a heterogeneous clinical presentation with no specific pathologic substratum. Its accurate diagnosis is a challenge for neurologists; in order to establish CBS definitively, postmortem confirmation is required. Some clinical and radiological features can help to distinguish it from other neurodegenerative conditions, such as Creutzfeldt-Jakob disease (CJD).

Clinical Case: A 74-year-old woman presented with language impairment, difficulty in walking and poor attentiveness that had begun 10 days before. Other symptoms, such as asymmetrical extra-pyramidal dysfunction, limb dystonia and ‘alien limb’ phenomena, were established over the next 2 months, with rapid progression. Death occurred 3 months after symptom onset. Laboratory results were normal. Initially, imaging only showed restricted diffusion with bilateral parieto-occipital gyri involvement on DWI-MRI, with unspecific EEG changes. An autopsy was performed. Brain neuropathology confirmed sporadic CJD (sCJD).

Conclusions: CBS is a heterogeneous clinical syndrome whose differential diagnosis is extensive. CJD can occasionally present with clinical characteristics resembling CBS. MRI detection of abnormalities in some sequences (FLAIR, DWI), as previously reported, has high diagnostic utility for sCJD diagnosis – especially in early stages – when other tests can still appear normal. Abnormalities on DWI sequencing may not correlate with neuropathological findings, suggesting a functional basis to explain the changes found.

Introduction

The core clinical characteristics of corticobasal syndrome (CBS) include findings suggesting cortical dysfunction (apraxia, ‘alien limb’ phenomena, cortical sensory loss, myoclonus, mirror movements) and basal ganglia dysfunction (bradykinesia, progressive asymmetric rigidity, dystonia, tremor) [1].

Subacute CBS-like disorder with rapid progression over a period of weeks has been described as a presentation form of sporadic Creutzfeldt-Jakob disease (sCJD) [2]. The clinical phenotype and progression of symptoms actually reflect the topographic distribution of histopathology more than the specific underlying histology [3]. Diffusion-weighted MRI images (DWI) can be sensitive enough in early stages of the disease for a differential diagnosis [4].

We present a CBS case which turned out to be sCJD on postmortem neuropathological study. Moreover, we discuss relevant MRI features which may also contribute to the diagnosis of sCJD while patients are still alive.

Clinical Case

A 74-year-old woman with previous hypertension and hypercholesterolemia was admitted to our hospital with a 10-day history of gait disturbance and reduced attentiveness. On initial examination, she appeared bradyphrenic with decreased verbal fluency and some comprehension mistakes. She was disoriented to time and had prominent dysgraphia. Immediate recall and short-term memory were also severely disturbed. She presented ideomotor and ideational apraxia, executive dysfunction as well as agrophesthesia and astereognosis with intact primary sensory modalities. Oculomotor function was normal except for an increased latency of saccadic eye movements.

Our patient’s left hand had a mainly dystonic posture, with forced wrist flexion. She had gait apraxia, and while speaking her right arm performed occasional aimless movements, wandering out of her view. No grasping or myoclonic jerks were noted. Mild cog-wheel rigidity and bradykinesia of the upper and lower limbs with right predominance were present. Cranial nerves, motor and cerebellar function and deep reflexes were otherwise normal. Over the next 4 weeks she became aphasic, incontinent and dysphagic, with severe rigidity and generalized myoclonus. Death occurred 3 months after symptomatology onset.

Laboratory tests, including a complete blood count, blood chemistry, thyroid function test, vasculitis markers, HIV and VDRL tests, and vitamin B12 and folate levels, were normal. Cerebrospinal fluid biochemistry was normal. Results were positive for 14-3-3 protein, and polymorphism testing at PRNP (human prion gene) codon 129 showed homozygosity for methionine (MM1). PRNP gene mutations were excluded. MRI performed 2 days after admission revealed bilateral hyperintensity of the cortical ribbon of the parieto-occipital cortex on T₂ sequences, with gyriiform enhancement on DWI (fig. 1). Initial electroencephalogram (EEG) showed a severe diffuse slowing. One month later, generalized sharp and triphasic waves with a periodic pattern of 1–1.5 Hz were present.

Autopsy was restricted to the encephalon. Macroscopically, moderate gyral frontal atrophy was present. On microscopic sections, the main lesions consisted of spongiform changes characterized by multiple round vacuoles within the neuropil in the cerebral cortex (occipital lobe, mainly), cerebellum molecular layer and basal ganglia (fig. 2a). Severe neuronal loss and reactive gliosis could also be seen along with the spongiform changes and even in places where such changes were minimal or absent. Immunohistochemistry for pathological prion protein (PrP^{Sc}-monoclonal mouse PrP, clone 3F4; Dako) showed extensive cerebral and cerebellar diffuse synaptic-like immunoreactivity (fig. 2b). sCJD was diagnosed.

Discussion

CBS encompasses different entities, such as corticobasal degeneration (CBD), Alzheimer disease, frontotemporal dementia or progressive supranuclear palsy [3]. CBD is a tauopathy whose clinical diagnosis can be difficult [5]. This limitation highlights the relevancy of other diagnostic procedures, such as MRI. On MRI, CBD patients may present asymmetric frontoparietal and midcallosal atrophy [6, 7]. Additionally, on T₂-weighted and fluid-attenuated inversion recovery (FLAIR) images, they may also show putaminal hypointensity and subtle subcortical periventricular hyperintensity [8, 9]. On DWI, extensive hyperintensity in the frontoparietal white matter, especially on the predominant side of cortical atrophy, has been described [8]. These features are especially evident in the early course of CBD [8].

sCJD is the most frequent human prion disease. Its diagnostic criteria include clinical characteristics and auxiliary investigations, such as EEG results and surrogate biomarkers in the cerebrospinal fluid [10]. However, definitive diagnosis is neuropathological [10], either by immunohistochemical evidence of pathogenic prion deposits, or by the typical migration profile of prion protein on Western blot.

In recent years, a series of publications has demonstrated a potentially important role for MRI, not only in diagnosing sCJD in living patients, but also in identifying its distinct molecular subtypes [10, 11]. The highest diagnostic accuracy is obtained by finding high signal abnormalities either in at least 2 cerebral cortical regions (temporal, parietal or occipital) or in the basal ganglia (both caudate nucleus and putamen) in FLAIR or DWI sequences [10–12]. Accordingly, an amendment to the classic criteria for sCJD has been proposed to include these MRI abnormalities [10]. While in sCJD the characteristic DWI appearance seems to be restricted to diffusion in the cortical ribbon and basal ganglia structures, in CBS hyperintensity in frontoparietal white matter, mainly on the predominant side of cortical atrophy, may be seen [10].

The pathophysiological basis for restricted diffusion in cases of spongiform encephalopathy remains unknown [13]. While some hypotheses propose that it is secondary to vacuoles or prion protein deposition on β -pleated sheet conformation [13], others interpret it as active gliosis [14].

Initially, our patient displayed symptoms of parietal dysfunction and acute dementia. Some typical clinical features of sCJD, such as pyramidal signs, ataxia, visual signs or myoclonus, were absent at this stage. CBS with symptoms and signs of higher cortical dysfunction has been reported previously as a presentation form of sCJD [2, 15, 16]. Parietal lobe dysfunction without dementia was present with basal ganglia signs in one case, as in our patient [16]. Also similar to our patient, nonsense hand movements without ‘foreign’ hand sensation have been described using the term ‘wayward hand’ [16]; such movements are related to a contralateral lesion of the supplementary motor area [17]. Disease duration in the other cases was longer (6 and 8 months, and 4 years, respectively) [13, 16, 18]. Nevertheless, protein 14-3-3 was negative in 2 of those cases, likely reflecting a focal neuronal destruction [13, 16]. MRI on long TR sequences (FLAIR, T₂) in 1 of the cases [16], as in ours with cortical ribbon hyperintensity, was helpful in diagnosis.

The DWI signal with bilateral parieto-occipital hyperintensities was in fact a useful and sensitive tool to distinguish between CJD and CBS, as reported before [4, 15].

Abnormalities seen on DWI usually correlate with clinical exam findings, but not necessarily closely with neuropathological findings, especially in early disease stages [4].

This case highlighted the classic neuropathological features of sCJD [19]. The severity of these abnormalities is usually related to disease duration, and this fact may have accounted for the paucity of spongiform change found in our patient. In addition to the conventional histopathological study, detection of extensive accumulation of pathological prion protein (PrP^{sc}) by immunohistochemistry confirmed the diagnosis [20]. The atypical clinical presentation and the utility of DWI or FLAIR signal changes in MRI as part of the sCJD diagnostic process are supported by this case.

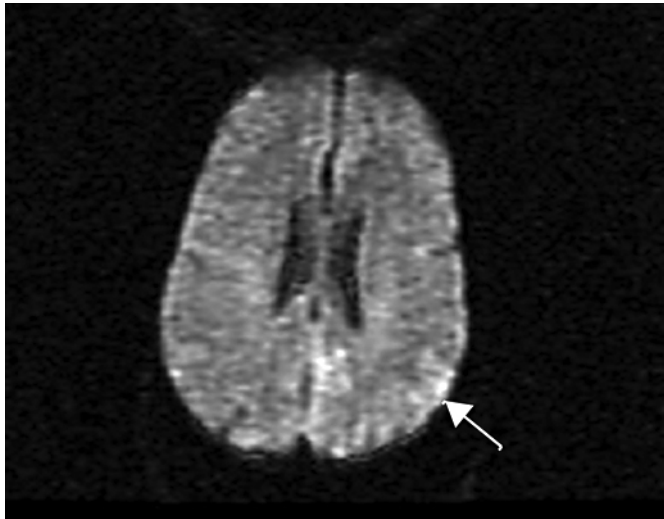


Fig. 1. DWI-MRI showing gyriform enhancement (white arrow).

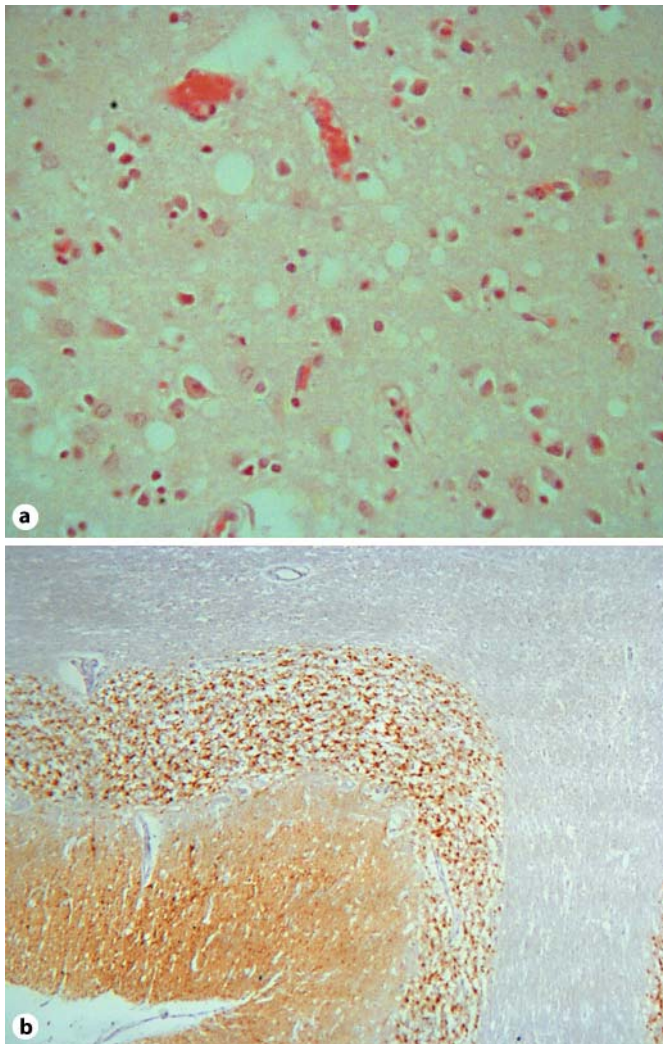


Fig. 2. **a** Occipital lobe – moderate cortical spongiform change and proliferation of reactive astrocytes. HE. $\times 40$ (original magnification). **b** Cerebellum – cortical deposits of pathogenic PrP in a diffuse synaptic pattern. Monoclonal antibody 3F4. $\times 40$ (original magnification).

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